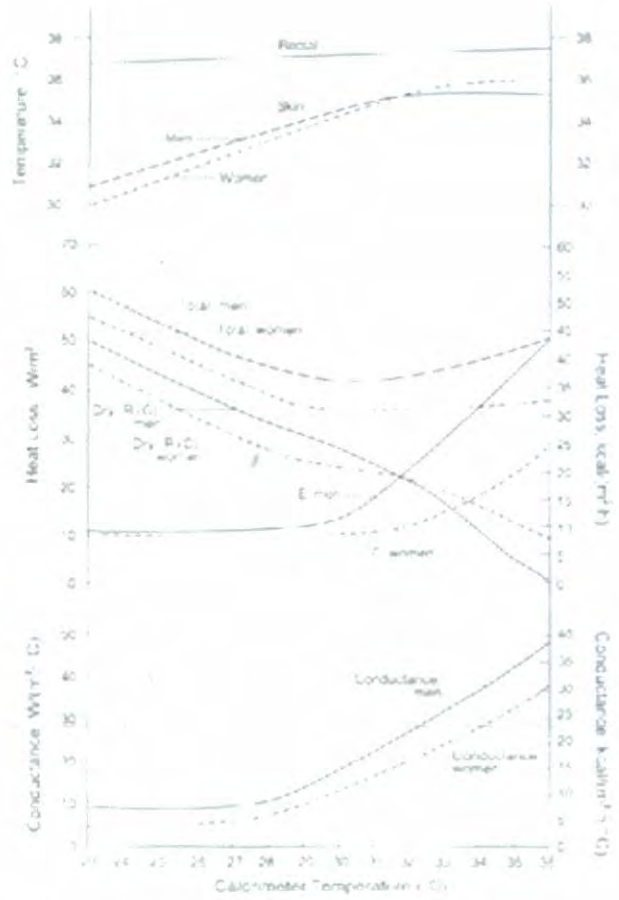

Fig. 2-9. Average values of rectal and mean skin temperatures, heat loss, and core-to-skin thermal conductance for nude resting men and women near steady state after 2 hours at different environmental temperatures in a calorimeter. (All energy-exchange quantities in this figure have been divided by body surface area, to remove the effect of individual body size.) Total heat loss is the sum of dry heat loss (by radiation [R] and convection [C]) and evaporative heat loss (E). Dry heat loss is proportional to the difference between skin temperature and calorimeter temperature, and it decreases with increasing calorimeter temperature. Adapted (data correction) with permission from Wenger CB. The regulation of body temperature. In: Rhoades RA, Tanner GA, eds. *Medical Physiology*. Boston, Mass: Little, Brown; 1995: 596. Data source: Hardy JD, DuBois EF. Differences between men and women in their response to heat and cold. *Proc Natl Acad Sci U S A*. 1940;26:389–398.

and mean skin temperatures, respectively.

At ambient temperatures below 28°C, these subjects' conductance is minimal because their skin blood flow is quite low. Because the minimum attainable level of conductance depends chiefly on the subcutaneous fat layer, the women's thicker layer allows them to attain a lower conductance than men. At about 28°C, conductance begins to increase, and above 30°C, conductance continues to increase and sweating begins. For these nude subjects, the range 28°C to 30°C is the zone of *thermoneutrality;* that is, the range of comfortable environmental temperatures in which thermal balance is maintained without either shivering or sweating.[12] In this zone, heat loss is matched to heat production by controlling conductance, and thus $\bar{T}_{sk}$, R, and C.

Evaporation

As we saw in Figure 2-9, evaporative heat loss is nearly independent of ambient temperature below 30°C, and is 9 to 10 W/m^2. This corresponds to evaporation of about 13 to 15 $g/(m^2 \bullet h)$, of which about half is lost through breathing and half as insensible perspiration. This heat loss is not under thermoregulatory control. To achieve heat balance at higher ambient temperatures, the subjects in Figure 2-9 depend more and more on evaporation of sweat, which in humans can dissipate large amounts of heat.

There are two histological types of sweat glands, *eccrine* and *apocrine*. In humans, apocrine glands are found mostly in the axilla, inguinal region, perianal skin, and mammary areolae, and less consistently on other parts of the trunk and the face.[22] Eccrine sweat is essentially a dilute electrolyte solution, but apocrine sweat also contains fatty material. Eccrine sweat glands are widely distributed and are the more important type in human thermoregulation, and functionally active eccrine glands number about 2 to 3 million.[23] They are controlled through postganglionic sympathetic nerves, which release acetylcholine[23] rather than norepinephrine. A healthy man unacclimatized to heat can secrete up to 1.5 liters of sweat per hour. Although the number of functional sweat glands is fixed before the age of 3 years,[23] the secretory capacity of individual glands can change, especially with endurance exercise training and heat acclimatization; and a man who is well acclimatized to heat can secrete more than 2.5 L/h.[24,25] Such rates cannot be maintained, however, and the maximum daily sweat output is probably about 15 L.[26]

Sodium concentration of eccrine sweat ranges from less than 5 to 60 mEq/L[27] (vs 135–145 mEq/L in plasma); but even at 60 mEq/L, sweat is one of the most dilute body fluids. To produce sweat that is hypotonic to plasma, the glands reabsorb sodium from the sweat duct by active transport. As sweat

rate increases, the rate at which the glands reabsorb sodium increases more slowly, so that sodium concentration in the sweat increases.

Skin Circulation and Dry (Convective and Radiative) Heat Exchange

Heat produced within the body must be delivered to the skin surface to be eliminated. When skin blood flow is minimal, core-to-skin thermal conductance (ie, the conductance of the shell) is typically 5 to 9 W per Centigrade degree per square meter of body surface (see Figure 2-9). A lean resting subject with a surface area of 1.8 m^2, minimal whole-body conductance of 16 W/°C [ie, 8.9 W/(°C • m^2) x (1.8 m^2)] and a metabolic heat production of 80 W, requires a temperature difference between core and skin of five Centigrade degrees (ie, 80 W ÷ 16 W/°C) to allow the heat produced inside the body to be conducted to the surface. In a cool environment, T_{sk} may easily be low enough for this to occur. However, in an ambient temperature of 33°C, $\overline{T}_{sk}$ is typically about 35°C; and without an increase in conductance, core temperature would need to rise to 40°C—a high although not yet dangerous level—for the heat to be conducted to the skin. But if the rate of heat production were increased to 480 W by moderate exercise, the temperature difference between core and skin would have to rise to 30°C—and core temperature to well beyond lethal levels—to allow all the heat produced to be conducted to the skin. In such circumstances a large increase in conductance is needed for the body to reestablish thermal balance and continue to regulate its temperature; and this is accomplished by increasing skin blood flow.

Role of Skin Blood Flow in Heat Transfer

If we assume that blood on its way to the skin remains at core temperature until it reaches the skin, comes to skin temperature as it passes through the skin, and then stays at skin temperature until it returns to the core, we can compute the rate of heat flow (HF_b) due to convection by the blood as seen in Equation 8:

$$(8) \quad HF_b = SkBF \bullet (T_c - T_{sk}) \bullet 3.85\ kJ/(L \bullet °C)$$

where *SkBF*, the rate of skin blood flow, is expressed in L/s rather than the more usual L/min, to simplify computing HF in W (ie, J/s); and *3.85 kJ/(L • °C) [0.92 kcal/(L • °C)]* = volume specific heat of blood[28] (see Table 2-2).

Conductance due to convection by the blood (C_b) is calculated as seen in Equation 9:

$$(9) \quad C_b = HF_b/(T_c - T_{sk}) = SkBF \bullet 3.85\ kJ/(L \bullet °C)$$

Of course, heat continues to flow by conduction through the tissues of the shell, so that total conductance is the sum of conductance due to convection by the blood plus that due to conduction through the tissues; and total heat flow is given by Equation 10:

$$(10) \quad HF = (C_b + C_0) \bullet (T_c - T_{sk})$$

in which C_0 is thermal conductance of the tissues when skin blood flow is minimal, and thus is due predominantly to conduction through the tissues.

The assumptions on which Equation 8 depend represent the conditions for maximum efficiency of heat transfer by the blood, and are somewhat artificial. In practice, blood also exchanges heat with the tissues through which it passes going to and from the skin. Heat is exchanged with these other tissues most easily when skin blood flow is low, and in such cases heat flow to the skin may be much less than that predicted by Equation 8. However, Equation 8 is a reasonable approximation in a warm subject with moderate-to-high skin blood flow. It is not possible to measure whole-body skin blood flow directly, but it is estimated to reach nearly 8 L/min during maximal cutaneous vasodilation.[29,30] Maximal cutaneous vasodilation does not occur during heavy exercise,[31] but skin blood flow still may reach several liters per minute during heavy exercise in the heat.[29] If SkBF = 1.89 L/min (0.0315 L/s), then, according to Equation 9, skin blood flow contributes about 121 W/°C to the conductance of the shell. If conduction through the tissues contributes 16 W/°C, total shell conductance is 137 W/°C; and if T_c = 38.5°C and T_{sk} = 35°C, then this will produce a core-to-skin heat transfer of 480 W, the heat production in our earlier example of moderate exercise. Thus even a moderate rate of skin blood flow can have a dramatic effect on heat transfer.

In a person who is not sweating, raising skin blood flow brings skin temperature nearer to blood temperature, and lowering skin blood flow brings skin temperature nearer to ambient temperature. In these conditions the body controls dry (convective and radiative) heat loss by varying skin blood flow and thus skin temperature. Once sweating begins, skin blood flow continues to increase as the person becomes warmer, but now the tendency of an increase in skin blood flow to warm the skin is approxi-

mately balanced by the tendency of an increase in sweating to cool the skin. Therefore, after sweating has begun, further increases in skin blood flow usually cause little change in skin temperature or dry heat exchange, and serve primarily to deliver to the skin the heat that is being removed by evaporation of sweat. Skin blood flow and sweating thus work in tandem to dissipate heat under such conditions.

Sympathetic Control of Skin Circulation

Blood flow in human skin is under dual vasomotor control.[8,30,32] In most of the skin the vasodilation that occurs during heat exposure depends on sympathetic nervous signals that cause the blood vessels to dilate, and this vasodilation can be prevented or reversed by regional nerve block.[33] Because it depends on the action of nervous signals, such vasodilation is sometimes referred to as active vasodilation. Active vasodilation occurs in almost all the skin except in the so-called acral regions—hands, feet, lips, ears, and nose.[34] In the skin areas where active vasodilation occurs, vasoconstrictor activity is minimal at thermoneutral temperatures; and as the body is warmed, active vasodilation does not begin until close to the onset of sweating.[30,35] Thus skin blood flow in these areas is not much affected by small temperature changes within the thermoneutral range.[34] The neurotransmitter or other vasoactive substance responsible for active vasodilation in human skin has not been identified.[36] However, because sweating and vasodilation operate in tandem in the heat, some investigators[30,37] have proposed that the mechanism for active vasodilation is somehow linked to the action of sweat glands.

Reflex vasoconstriction, which occurs in response to cold and also as part of certain nonthermal reflexes such as baroreflexes, is mediated primarily through adrenergic sympathetic fibers, which are distributed widely over most of the skin.[36] Reducing the flow of impulses in these nerve fibers allows the blood vessels to dilate. In the acral regions[30,36] and in the superficial veins,[30] vasoconstrictor fibers are the predominant vasomotor innervation, and the vasodilation that occurs during heat exposure is largely a result of the withdrawal of vasoconstrictor activity.[34] Blood flow in these skin regions is sensitive to small temperature changes even in the thermoneutral range, and may be responsible for "fine tuning" heat loss to maintain heat balance in this range.

THERMOREGULATORY CONTROL

In control theory, the words *regulation* and *regulate* have meanings distinct from those of *control*. A control system acts to minimize changes in the *regulated* variable (eg, core temperature) that are produced by disturbances from outside the system (eg, exercise or changes in the environment) by making changes in certain other variables (eg, sweating rate, skin blood flow, metabolic rate, and thermoregulatory behavior), which are called *controlled* variables. Human beings have two distinct subsystems to regulate body temperature: behavioral thermoregulation and physiological thermoregulation. Physiological thermoregulation is capable of fairly precise adjustments of heat balance but is effective only within a relatively narrow range of environmental temperatures. On the other hand, behavioral thermoregulation, through the use of shelter and space heating and clothing, enables humans to live in the most extreme climates on earth, but it does not provide fine control of body heat balance.

Behavioral Thermoregulation

Behavioral thermoregulation is governed by thermal sensation and comfort. Sensory information about body temperatures is an essential part of both behavioral and physiological thermoregulation. The distinguishing feature of behavioral thermoregulation is the direction of conscious effort to reduce discomfort. Warmth and cold on the skin are felt as either comfortable or uncomfortable, depending on whether they decrease or increase the physiological strain.[38] Thus a shower temperature that feels pleasant after strenuous exercise may be uncomfortably cold on a chilly morning. Because of the relation between discomfort and physiological strain, behavioral thermoregulation, by reducing discomfort, also acts to minimize the physiological burden imposed by a stressful thermal environment. For this reason the zone of thermoneutrality is characterized by thermal comfort as well as by the absence of shivering and sweating.

The processing of thermal information in behavioral thermoregulation is not as well understood as it is in physiological thermoregulation. However, perceptions of thermal sensation and comfort respond much more quickly than either core temperature or physiological thermoregulatory responses to changes in environmental temperature,[39,40] and thus appear to anticipate changes in the body's ther-

mal state. Such an anticipatory feature presumably reduces the need for frequent small behavioral adjustments.

Physiological Thermoregulation

Physiological thermoregulation operates through graded control of heat-production and heat-loss responses. Familiar nonliving control systems, such as most refrigerators and heating and air-conditioning systems, operate at only two levels because they act by turning a device on or off. In contrast, most physiological control systems produce a response that is graded according to the disturbance in the regulated variable. In many physiological systems, changes in the controlled variables are proportional to displacements of the regulated variable from some threshold value, and such control systems are called *proportional control* systems.

The control of heat-dissipating responses is an example of a proportional control system.[9] Figure 2-10 shows how reflex control of sweating and skin blood flow depends on body core and skin temperatures. Each response has a core temperature threshold, a temperature at which the response starts to increase; and these thresholds depend on mean skin temperature. Thus at any given skin temperature, the change in each response is proportional to the change in core temperature; and increasing the skin temperature lowers the threshold level of core temperature and increases the response at any given core temperature. In humans, a change of one Centigrade degree in core temperature elicits about nine times as great a thermoregulatory response as a change in mean skin temperature of one Centigrade degree.[8] (Besides its effect on the reflex signals, skin temperature has a local effect that modifies the blood vessel and sweat gland responses, as discussed later.)

Integration of Thermal Information

The central nervous system integrates thermal information from core and skin. Receptors in the body core and the skin transmit information about their temperatures through afferent nerves to the brainstem, and especially the hypothalamus, where much of the integration of temperature information occurs.[41] The sensitivity of the thermoregulatory responses to core temperature allows the thermoregulatory system to adjust heat production and heat loss to resist disturbances in core temperature. Their sensitivity to mean skin temperature allows the system to respond appropriately to mild heat or cold exposure with little change in body core temperature, so that environmentally induced changes in body heat content occur al-

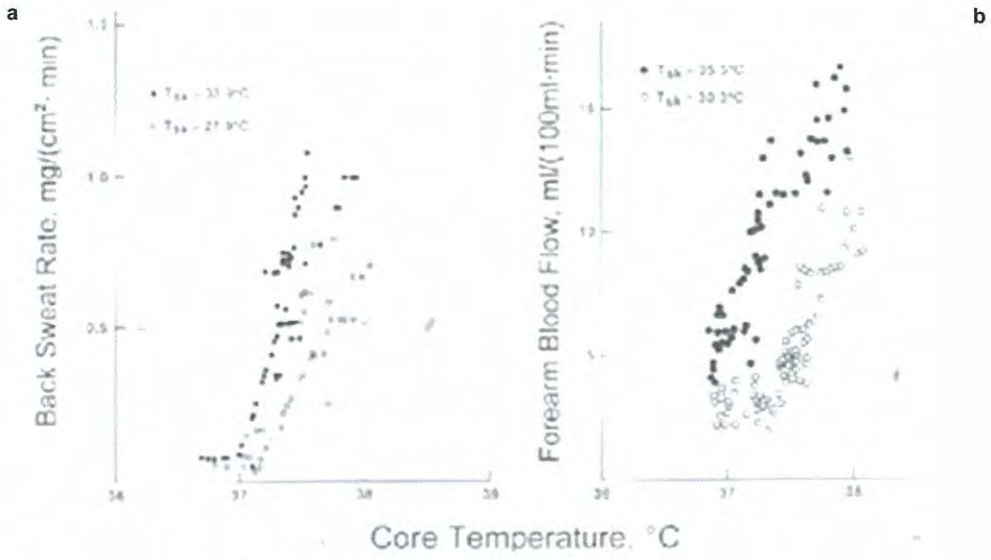

Fig. 2-10. The relations of (**a**) back (scapular) sweat rate and (**b**) forearm blood flow to core temperature and mean skin temperature ($\bar{T}_{sk}$). In the experiments shown, core temperature was increased by exercise. Adapted with permission from Sawka MN, Wenger CB. Physiological responses to acute exercise–heat stress. In: Pandolf KB, Sawka MN, Gonzalez RR, eds. *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes.* Indianapolis, Ind: Benchmark Press (now Cooper Publishing Group, Carmel, Ind); 1988: 101.

most entirely in the peripheral tissues (see Figure 2-2). For example, when someone enters a hot environment, his or her skin temperature rises and may elicit sweating even if there is no change in core temperature. On the other hand, an increase in heat production due to exercise elicits the appropriate heat-dissipating responses through a rise in core temperature.

Core temperature receptors involved in the control of thermoregulatory responses are concentrated especially in the hypothalamus,[42] but temperature receptors in other core sites, including the spinal cord and medulla, also participate.[42] The anterior preoptic area of the hypothalamus contains many neurons that increase their firing rate either in response to warming or in response to cooling, and temperature changes in this area of only a few tenths of a Centigrade degree elicit changes in the thermoregulatory effector responses of experimental mammals. Thermal receptors have been reported elsewhere in the core, including the heart, pulmonary vessels, and spinal cord; but the thermoregulatory role of core thermal receptors outside the central nervous system is not known.[8]

Let us consider what happens when a disturbance—say, an increase in metabolic heat production due to exercise—upsets the thermal balance. Heat is stored in the body, and core temperature rises. The thermoregulatory controller receives information about these changes from the thermal receptors, and responds by calling forth appropriate heat-dissipating responses. Core temperature continues to rise, and these responses continue to increase until they are sufficient to dissipate heat as fast as it is being produced, thus restoring heat balance and preventing further increases in body temperatures. The rise in core temperature that elicits heat-dissipating responses sufficient to reestablish thermal balance during exercise is an example of a *load error*[9]; a load error is characteristic of any proportional control system that is resisting the effect of some imposed disturbance or "load." Although the disturbance in this example was exercise, parallel arguments apply if the disturbance is a change in the environment, except that most of the temperature change will be in the skin and shell rather than in the core.

Relation of Effector Signals to Thermoregulatory Set Point

Both sweating and skin blood flow depend on core and skin temperatures in the same way, and changes in the threshold for sweating are accompanied by similar changes in the threshold for vasodilation.[4] We may therefore think of the central integrator (Figure 2-11) as generating one thermal command signal for the control of both sweating and skin blood flow. This signal is based on the information about core and skin temperatures that the integrator receives, and on the thermoregulatory *set point*.[4] We may think of the set point as the target level of core temperature, or the setting of the body's "thermostat." In the operation of the thermoregulatory system, it is a reference point that determines the thresholds of all the thermoregulatory responses.

Nonthermal Influences on Thermoregulatory Responses

Each thermoregulatory response may be affected by other inputs besides body temperatures and factors that affect the thermoregulatory set point. Nonthermal factors may produce a burst of sweating at the beginning of exercise,[43,44] and the involvement of sweating and skin blood flow in emotional responses is familiar to everyone.

Of the thermoregulatory responses that are important during heat stress, skin blood flow is most affected by nonthermal factors because of its involvement in reflexes that function to maintain cardiac output, blood pressure, and tissue oxygen delivery during heat stress, postural changes, and hemorrhage, and sometimes during exercise, especially in the heat.

Physiological and Pathological Changes to the Thermoregulatory Set Point

Several physiological and pathological influences change the thermoregulatory set point. Fever elevates core temperature at rest, heat acclimatization decreases it, and time of day and phase of the menstrual cycle change it in a cyclical fashion.[4–6] Core temperature at rest varies with time of day in an approximately sinusoidal fashion, reaching a minimum at night, several hours before awaking, and a maximum—which is one half to one Centigrade degree higher—in the late afternoon or evening (see Figure 2-3). Although this pattern coincides with patterns of activity and eating, it is independent of them, occurring even during bed rest and fasting. This pattern is an example of a *circadian* rhythm (ie, a rhythmic pattern in a physiological function with a period of about 1 day). During the menstrual cycle, core temperature is at its lowest point just before ovulation; over the next few days it rises one-half to one Centi-

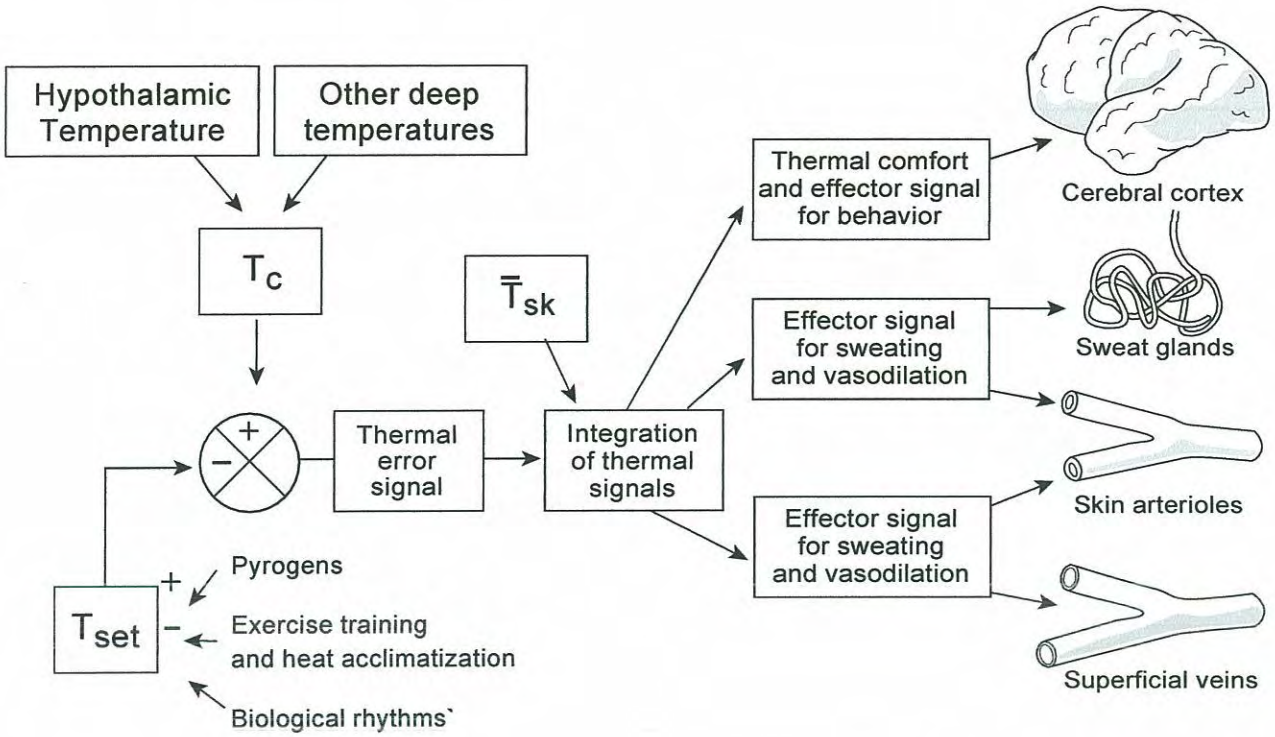

Fig. 2-11. Schematic diagram of the control of human thermoregulatory responses. The signs by the inputs to T_{set} indicate that pyrogens raise the set point, and heat acclimation lowers it. Core temperature, T_c, is compared with the set point, T_{set}, to generate an error signal, which is integrated with thermal input from the skin to produce effector signals for the thermoregulatory responses. Adapted with permission from Sawka MN, Wenger CB. Physiological responses to acute exercise-heat stress. In: Pandolf KB, Sawka MN, Gonzalez RR, eds. *Human Performance Physiology and Environmental Medicine at Terrestrial Extremes*. Indianapolis, Ind: Benchmark Press (now Traverse City, Mich: Cooper Publishing Group); 1988: 97–151.

grade degree and remains elevated for most of the luteal phase. Each of these factors—fever, heat acclimatization, the circadian rhythm, and the menstrual cycle—affects core temperature at rest by changing the thermoregulatory set point, thus producing corresponding changes in the thresholds for all the thermoregulatory responses.

Peripheral Modification of Skin Vascular and Sweat Gland Responses

The skin is the organ most directly affected by environmental temperature, and skin temperature affects heat loss responses not only through the reflex actions shown in Figure 2-10 but also through direct effects on the effectors themselves. Local temperature changes act on skin blood vessels in at least two ways. First, local cooling potentiates (and heating weakens) the constriction of blood vessels in response to nervous signals and vasoconstrictor substances.[36] Second, in skin regions where active vasodilation occurs, local heating dilates the blood vessels (and local cooling constricts them) through a direct action that is independent of nervous signals.[45,46] This effect is especially strong at skin temperatures above 35°C[46]; and when the skin is warmer than the blood, increased blood flow helps to cool the skin and protect it from heat injury.

The effects of local temperature on sweat glands parallel those on blood vessels, so that local heating magnifies (and local cooling reduces) the sweating response to reflex stimulation or to acetylcholine,[37] and intense local heating provokes sweating directly, even in sympathectomized skin.[47] During prolonged (several hours) heat exposure with high sweat output, sweat rates gradually diminish, and the sweat glands' response to locally applied cholinergic drugs is reduced also. The reduction of sweat gland responsiveness is sometimes called *sweat gland "fatigue."* Wetting the skin makes the stratum corneum swell, mechanically obstructing the sweat duct and causing a reduction in sweat